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EXAMINER

PORTNER, VIRGINIA ALLEN

ART UNIT

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1645

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/693,377

**Applicant(s)**

BOONE ET AL.

**Examiner**

GINNY PORTNER

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3, 6-12, 15-17, 20, 24 and 27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6-12, 15-17, 20, 24 and 27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_



### DETAILED ACTION

Amended claims 1-3, 6-12, 15-17, 20, 24 and 27 are pending.

#### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 1, 2008 has been entered.

#### *Objections/Rejections Withdrawn*

2. **Rejection Withdrawn** The rejection of claims 13-14, 17-18 and 21-23 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements (presented in paragraph 9, page 4 of the Office Action dated mailed February 22, 2007) is herein withdrawn in light of some claims having been canceled and other amended to recite the essential elements ie. "enzyme-linked antibody".
3. **Claim Objections** Claims 13 and 14 objected to because of the following informalities is herein withdrawn in light of both claims having been canceled.
4. The rejection of claims 1-3, 6-22, 24 and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is herein withdrawn in light of the claims having been amended to no longer recite the phrase "other than a breast-fed infant".
5. The rejection of claims 14, 19 and 22 under 35 U.S.C. 112, second paragraph, for reciting the phrase/term "corresponds to the level" has been obviated by cancellation of the claims.
6. The rejection of claim 3 under 35 U.S.C. 112, second paragraph, for reciting the phrase "diagnosis of irritable bowel syndrome" has been obviated by amending claim 3 to directly depend from claim 1 which is directed to a method of diagnosis (preamble)
7. The rejection of claim 23 under 35 U.S.C. 112, second paragraph, for reciting the phrase "an enzyme linked antibody bound" has been obviated by canceling claim 23.

**Please Note:** Claim 1 is being read to encompass the measurement of lactoferrin in fecal samples obtained from subjects that have the common symptom of diarrhea, and a sample that does not evidence elevated lactoferrin is encompassed by claim 1 to determine the possible presence of irritable bowl syndrome in light of claim 3 having been amended to directly depend from

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independent claim 1. Diagnosis of irritable bowel syndrome (IBS) would not require the measurement of ANCA and ASCA antigens in the method of claim 1, because lactoferrin in IBS is not elevated. Therefore, in light of claim 3 depending directly from claim 1, claim 1 is only required to carry out the obtaining and measuring steps for lactoferrin in fecal samples used in diagnosis of IBS. No additional steps would be required to be carried out on an IBS sample, as the sample would not be selected for additional measurement, as it would not have elevated lactoferrin levels in it by definition.

***Rejections Maintained/Response to Arguments***

1. Applicant's arguments filed May 1, 2008 have been fully considered but they are not persuasive.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Rejection Maintained , Claim 8 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is traversed on the grounds that the claim as amended is clear; the claim now recites the phrase “for capturing fragments”.
4. It is the position of the examiner that while amended, Claim 8 still recites the phrase “capturing fragments”; what these fragments are is unclear; what fragments are being captured? No fragments are defined in amended independent claim 1, from which claim 8 depends; what are the fragments in the sample. What are the captured fragments?

***Double Patenting***

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. The rejection of claims 1, 3, 11-12, 15-16 and 24 provisionally on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 2004/0033537 (10/629,975) is traversed by Applicant that the grounds of rejection be held in abeyance until allowable subject matter is indicated.

7. The examiner is maintaining the rejection for reasons of record.

8. The rejection of claims 1, 3, 11, 12 15-16 and 24 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 7,192,724) is traversed by Applicant that the grounds of rejection be held in abeyance until allowable subject matter is indicated.

9. The examiner is maintaining the rejection for reasons of record.

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10. The rejection of claims 1-2, 3, 6-12, 15-17,20 provisionally on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7-14 of copending Application No. PG-pub 2004,0126898 (10/656,034) ) is traversed by Applicant that the grounds of rejection be held in abeyance until allowable subject matter is indicated.

11. The examiner is maintaining the rejection for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending species anticipates the instantly claimed genus of methods, wherein the instant claims do not require the measurement of specific type of immunoglobulin antibodies as claimed in copending claim 13 that measures IgG, IgE, IgM, IgD, IgAse, IgA and lactoferrin is disclosed to be elevated in subject with disease activity: **[0018] There were 51 ulcerative colitis (UC) patients, 47 Crohn's disease (CD) patients, 7 irritable bowel patients (IBS), and 11 healthy (H) adults recruited for the study. Fecal specimens were collected from each enrolled patient and stored at -70.degree. C. until tested. Specimen consistency ranged from solid to liquid. The level of fecal ANCA was determined using the qualitative ANCA ELISA as previously described. Disease activity was defined using elevated fecal lactoferrin as an indicator of intestinal inflammation. A dilution of 1:10 was used in the qualitative ELISA test and results were reported as positive (absorbance values >0.140) or negative (absorbance values <0.140). The mean optical densities, standard deviation and P values (two-tailed student T-test with unequal variance) were determined for the ANCA positive ulcerative colitis patients. Of the 26 patients that tested positive for fecal ANCA, there were four patients had Crohn's Disease, 21 had ulcerative colitis and one patient was healthy. ANCA-positive ulcerative colitis showed a mean.+-SD OD.sub.450 of 0.311.+-0.166. The mean optical density for the ulcerative colitis patients was significantly different from IBS and healthy persons (p value<0.0005). A summary of the statistical analysis is listed in Table 2.This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.**

12. ***Maintained, Claim Rejections - 35 USC § 102*** The rejection of claims 1, 3, 8-11, 15 and 24 under 35 U.S.C. 102(b) as being anticipated by Guerrant et al (US Pat. 5,124,252) is traversed on the grounds that:

- a. That Guerrant et al does not determine the presence of ASCA and ANCA and
- b. determines whether lactoferrin is present in the sample.

13. It is the position of the examiner that Guerrant measured the presence or absence of lactoferrin in a fecal sample, relative to control samples that were all negative on 7 different occasions (see quoted section Guerrant et al, col. 4, lines 12-22, specifically lines 20-22

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sion was stored at 4.C until used. Studies with titrations or purified lactoferrin revealed readily apparent agglutination of these latex beads with 0.004–0.0016 mg/ml lactoferrin, at least one log more sensitive than the radial immunodiffusion (RID) assay mentioned above. This level of greater sensitivity of latex agglutination was also seen with ficol-hypaque separated human PMN's as well with a 1:100 dilution being positive when RID detected only a 1:8 dilution. In addition, leukocytes added to stools as well as the *Salmonella* and 4 *C. difficile* cases were positive in the latex agglutination assay. Furthermore, three additional control specimens tested on 7 different occasions were all negative. Importantly, these immunoassay results remained clearly positive even after *C. difficile* cytotoxin totally destroyed the PMN morphology over 24 hours in refrigerated specimens.

14. Additionally, Guerrant et al claims a method of differentiating inflammatory diarrhea from noninflammatory diarrhea, diarrhea being a common symptom held in common between inflammatory bowel disease and irritable bowel syndrome (see Guerrant et al, claim 1). Nine of 12 samples from children with diarrhea were measured and found to have of lactoferrin that were not elevated, specifically titers of less than 1:50 (see quoted section below). No additional methods steps of selecting and measuring were/are required to diagnosis irritable bowel syndrome (instant claim 3), the 9 samples from children without elevated levels of lactoferrin anticipate the claimed invention set forth in claims 1 and 3 which is associated with a non-inflammatory process arising from the upper small bowel (see Guerrant et al, col. 1, lines 21-22 and claim 1), and unelevated levels of lactoferrin, which is claimed to be diagnostic of IBS.



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Further data from children with diarrhea in the northeast of Brazil have shown that specimens from 16 of 17 children with 114.5 or more fecal leukocytes per high power field on microscopy with methylene blue stain had lactoferrin latex agglutination titers of  $\geq 1:50$ . In contrast, only 3 of 12 methylene blue stained specimens with less than 1 leukocyte per high power field had lactoferrin titers of  $\geq 1:50$ . Furthermore, despite occasional positives at lower titers, none of 7 specimens from normal control children had lactoferrin titers of  $\geq 1:50$ .

Both quantitative and qualitative methods are described based upon relative titer (above) and specific ELISA sensitivity values (below, Guerrant et al, col. 4, lines 50-53)

- 1) **The apparent sensitivity was 0.001 ug/ul or less lactoferrin, with conjugate dilution of 1000 and primary rabbit antibody dilutions of 1:250, probably representing the optimal conditions for assay. The ELISA technology could also be employed in detection of leukocytes, possibly using a dipstick technology.**

15. Claims 1 and 24 while amended, only carries out the determining steps for ASCA and ANCA when the lactoferrin determination is POSITIVE and ELEVATED. Guerrant et al was applied against the claims for when the patient sample is negative or lactoferrin is present with unelevated lactoferrin levels. When the samples are negative, the additional tests are not required by the claims. With respect to claim 24, when the lactoferrin level is not elevated, Guerrant et al determines that the patient has non-inflammatory diarrhea, a symptom of irritable bowel syndrome. While Guerrant et al (see preamble of allowed claims) does not refer to non-inflammatory diarrhea as irritable bowel syndrome, a patient that presents with diarrhea and does not have elevated levels of lactoferrin, would not have inflammatory bowel disease, and would be a patient with irritable bowel. Therefore Guerrant et al still anticipates the instantly claimed invention as now claimed, for reasons of record and responses set forth herein.

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16. Claims 1, 3, 8-11, 15 (depends from claim 10) and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerrant et al (US Pat. 5,124,252).

Instant claim 1 and 24: Guerrant et al disclose the instantly claimed invention directed to a method, the method comprising the steps of:

17. obtaining a fecal sample from a person (see abstract);

18. determining whether lactoferrin is present in the sample (three additional control specimens tested on 7 different occasions were all negative (see col. 3, lines 63-64) and 9 of 12 samples did not evidence elevated levels of lactoferrin, the samples obtained from children with diarrhea.

**Instant claim 8-10:** wherein the presence of lactoferrin is measured by ELISA (see col. 4, lines 23-60, especially lines 30-31). **Instant claim 11:** further comprising diluting the sample (see col. 2, lines 38-42 "mixed with an equal amount of 0.1% Triton-X").

**Instant claim 12:** further comprising contacting the sample with immobilized polyclonal antibodies "Bacto-latex beads were coated with rabbit anti-human lactoferrin" and this latex bead suspension was added to "22 fecal specimens (see col. 4, lines 1-11), the endogenous lactoferrin being released by the leukocytes (see col. 4, lines 12-16 "children with diarrhea in the northeast of Brazil"). further comprising contacting said treated sample with enzyme linked polyclonal antibodies to create a readable sample (see col. 4, lines 42-44 "peroxidase conjugation", read both visually and spectrophotometrically (see col. 4, line 49 and claim 4). While the reference is silent with respect to whether the rabbit antibodies are polyclonal or monoclonal antibodies, it is clear that the reference does not discuss nor describe the production of hybridoma and monoclonal production, therefore the antibodies are conventional rabbit sera that comprise polyclonal antibodies.

**Instant claim 15:** further comprising generating a purified lactoferrin standard curve (see col. 4, lines 29-32, varying concentrations of lactoferrin were coated in the wells). The sensitivity of the assay was 0.001 ug/ml or less lactoferrin (see claim 4). Guerrant et al (US Pat. 5,124,252) anticipates the instantly claimed invention that does not require the claimed method to measure anything more than endogenous lactoferrin when the sample when the lactoferrin determination is considered negative in light of all the claims reciting the phrase "if so", which makes the following methods steps optional. Guerrant et al (US Pat. 5,124,252) anticipates the instantly claimed invention as now claimed.

19. The rejection of claims 1, 3, 11 and 24, 27 under 35 U.S.C. 102(b) as being anticipated by Fine et al (AJG, 1998) was not addressed or traversed on the record and therefore maintained for reasons of record.

**Instant claim 1, 3 and 24, 27:** Fine et al disclose the instantly claimed invention directed to a method, the method comprising the steps of:

20. obtaining a fecal sample from a person (see page 1301, col. 2, first two paragraphs);

21. determining whether lactoferrin is present in the sample (see page 1302, Table 1 "Diagnoses in 92 Patients with a negative fecal lactoferrin Test",

**Instant claim 27:** one patient's test changed levels upon repeating the lactoferrin determination (see page 1302, Table 1, bottom of ledger narrative). The lactoferrin data was used to distinguish the patients that have inflammatory bowel disease or syndrome from those patients that have another bowel condition (see page 1302, Table 1).

**Instant claim 11:** further comprising diluting the sample (see page 1301, col. 2, paragraph 3); further comprising contacting the sample with immobilized polyclonal antibodies latex beads were coated with rabbit anti-human lactoferrin, the endogenous lactoferrin is detected with the immobilized polyclonal antibodies. While the reference is silent with respect to whether the rabbit antibodies are polyclonal or monoclonal antibodies, it is clear that the

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reference does not discuss nor describe the production of hybridoma cell lines and monoclonal antibody production, therefore the antibodies are present in conventional rabbit sera that comprise polyclonal antibodies.

Fine et al anticipates the instantly claimed invention that does not require the claimed method to measure anything more than endogenous lactoferrin when the lactoferrin determination is considered not elevated in light of claim 3 being directed to diagnosis of IBS which does not require the additional selecting and measuring steps of claim 1 or claim 24, which makes the following methods steps optional. Fine et al still anticipates the instantly claimed invention as now claimed.

**22. Maintained, Claim Rejections - 35 USC § 103** *The rejection of claims 1-3,6-10, 24 and 27 under 35 U.S.C. 103(a) as being unpatentable over Nielsen et al (2000) in view of Targan et al (1995) and Fine (PG-Pub 2001/0036639A1, filing date March 2, 2001) is traversed on the grounds that:*

- c. Nielsen et al disclose testing for ASCA and ANCA in a serum sample,
- d. the sample of Targan is a serum sample and
- e. Fine does not teach elevated levels of ANCA or ASCA in a fecal sample.

**23.** In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

1. It is the position of the examiner that Nielsen et al teach Lactoferrin to be a fecal marker for inflammatory bowel disease (see page 360, col. 2, lines 3-5) and the importance of measuring ASCA and ANCA for distinguishing UC from Crohn's disease..

2. Nielsen et al additionally teaches the importance of distinguishing between inflammatory bowel disease patients, specifically distinguishing between ulcerative colitis (UC) and Crohn's disease (CD)(see page 359, col. 2, middle of second paragraph). Nielsen et al goes on to teach that pANCA is more common in UC than CD (see page 361, col. 2, paragraph 1) and that ASCA,

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antibodies to *Saccharomyces cerevisiae*, also known as bakers yeast, is a marker for Crohn's disease (see page 361, col. 2, paragraph 2). Nielsen et al teaches the combined measurement (see page 361, col. 2, p. 3) of both ANCA and ASCA in order to gain insight into sub classification of inflammatory bowel disease patients. Therefore, Nielsen et al clearly teaches measuring all three markers for assessment of disease activity in inflammatory bowel disease patients. The examiner agrees Nielsen et al is not applicable to the claims under 35 USC 102, but was applied against the claims under 35 USC 103, in view of guidance and teaching provided by Targan and Fine.

3. Applicant states that Targan et al analyze serum samples and do not teach elevated levels of ANCA in a fecal sample.

4. It is the position of the examiner that ANCA autoimmune antibodies are not normal antibodies that would not be present in a normal subject sample, and present in a subject with a disease condition. Detectable levels of ANCA would be elevated, over normal which would be undetectable.

It is also the position of the examiner that Targan et al clearly teach the intestinal B cells to be the source of serum antibodies, the intestinal B cells expressing pANCA are associated with fecal material into which they would express pANCA antibodies. The person of ordinary skill in the art would have been motivated and had a reasonable expectation of success of measuring pANCA antibodies in a fecal sample from a patient with UC as Targan et al teach 70% of UC patient produce pANCA antibodies from B cells from an intestinal sample.

5. Targan et al states ANCA is found in serum of ulcerative colitis patients, and focuses on measuring ANCA antibodies produced by B-cells in the colonic mucosa (see page 3262, col. 2, last sentence). The purpose of Targan et al's study is defined in col. 1, paragraph 1, on page 3263 where Targan et al found pANCA expressing cells in the mucosa of intestinal tissue (see patient population, sample were obtained from intestinal tissue, page 3263, col. 1, paragraph 2).

Figure 1 and Table 1 on page 3264 show patients with diverticulitis (non-IBD) and Crohn's disease to not significantly produce ANCA antibodies, while ANCA antibodies are significantly produced in UC patients. On page 3265, Discussion section, Targan et al state that "This study demonstrate the presence of ANCA-secreting B-cells within the mucosal LPL fraction from 70% of patients with UC." Targan et al cite two additional studies that support their finding that "the intestinal mucosa may be a unique source of autoantibody producing B-cells". One of these results "indicates that B cells may be directly activated in the mucosal compartment by enteric Ags, and suggests that the presence of Ab in serum is due to spill over of that production." Therefore, antibodies in fecal samples would not only come from the serum, but from B cells producing antibodies in the mucosal compartment of the intestine (see page 3265, col. 2, middle and end of first paragraph). Targan et al in summarizing their work states that their study indicated that "pANCA are being produced by local B cell populations within the lamina propria and are limited to mucosal tissues from UC patients", as well as states "Under appropriate conditions that result in chronic inflammation, such as are found in ileal pouches (ie., bacterial overgrowth and/or fecal stasis), these B cells are triggered to express pANCA.(page 3266, col. 2, first paragraph)" .

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24. It is the position of the examiner that Fine et al teach the presence of ASCA antibodies can be measured/determined in fecal samples. With respect to differential diagnosis of irritable bowel syndrome and inflammatory bowel disease, Fine et al teaches the essential criteria for differentiating these two conditions. Additionally, Fine et al still teaches the detection, measurement of ASCA antibodies from bakers' yeast which is also taught by Nielsen et al to be the source of these auto antibodies, the yeast being *Saccharomyces cerevisiae* (see Nielsen page 381, col. 2, p. 2). Clearly Nielsen et al and Fine et al are analogous art,

25. Nielson et al describe biological activity markers of Inflammatory Bowel Disease (see title, page 359), wherein the markers include fecal lactoferrin (see page 360, col. 2, paragraph 1), and auto antibodies known as ANCA and ASCA (see page 361, col. 1-2). Nielson et al teach the methods step of :

Obtaining a fecal sample from a patient and determining the presence of fecal lactoferrin (see page 360, col. 2, paragraph 1) in order to provide for both sensitive and bowel-specific markers of disease, and further determining the presence or absence of ASCA and ANCA in the patient (see page 361, col. 1-2).

Nielson et al teach the importance of assessing disease activity in inflammatory bowel disease (IBD), to include ulcerative colitis and Crohn's disease based upon clinical parameters and various biological disease markers (see page 359, col. 1, abstract, first sentence), but differs from the instantly claimed invention by failing to determine ANCA and ASCA in the fecal sample.

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Targan et al (1995) teach ANCA antibodies are presenting mucosal lesions of the bowel (whole abstract; and page 3266, col. 2, paragraph 1) in ulcerative colitis patients (non-serum samples, see table II, page 3265; p3264, Figure 1, Table 1; diluted 1:2 (see page 3264, Results section, first paragraph) in an analogous art for the purpose of quantitatively (see Table 1, page 3264, col. 5) defining pANCA production is a consequence of a mucosal immune response associated with ulcerative colitis (full last sentence of abstract; Fig. 1, p 3264). Fine et al (20010036639) teach a method of measuring fecal antibodies directed to *Saccharomyces* pervasive (ASCA) (see claims 1, 19-21 and 43; [0054]) in an analogous art for the purpose of determining the presence of antibodies associated with diseases or disorders of the bowel, to include diagnosis of irritable bowel syndrome (see page 3, [0020] and [0015; 0018, entire paragraph, as well as second half of paragraph. "diarrhea" ]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to measure fecal lactoferrin, ANCA and ASCA in a patient fecal sample because Nielson et al teach biological markers associated with inflammatory bowel disease, and teach fecal lactoferrin, as well as ANCA and ASCA to provide insight into disease activity associated with inflammatory bowel disease (see Nielsen et al, abstract, page 360, col. 2, p.1 and page 361, col. 1-2) and Targan et al and Fine et al teach the presence of ANCA and ASCA markers, respectively, are present in fecal/mucosal bowel samples and could be measured in the patient fecal sample along with the fecal lactoferrin determination. The person of ordinary skill in the art would have been motivated to determine fecal lactoferrin, along with fecal ANCA and ASCA markers because Nielsen et al teach that the lactoferrin is a measure of active bowel disease and measurement of ANCA and ASCA provide for differential diagnosis of the patient's type of inflammatory bowel disease (see Nielsen et al, page 361, col. 2, paragraph 3).

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of determining the presence or absence of inflammatory bowel disease (see page 360, col. 1, p. 1) by determining the fecal lactoferrin test, a marker for active bowel inflammatory disease, as taught by Nielsen et al, and if positive, further determining the presence and amount of ANCA and ASCA antibodies in the fecal sample because Nielsen et al teach that the "combined measurement of pANCA and ASCA may be used advantageously in the sub-classification of IBD patients with indeterminate colitis. Both antibody specificities are measured by traditional quantitative solid phase immunosorbent assays, and they are highly specific (>90%) for both UC and CD with disease sensitivity around 50% in both cases (see Nielsen et al, page 361, col. 2, paragraph 3)."



Nielsen et al in view of Targen et al and Fine et al obviate the instantly claimed invention as now claimed.

***New Claim Limitations/New Grounds of Objection/ Rejection***

***Claim Objections***

26. Claims 1 and 12 are objected to because of the following informalities:

- Claim 1 recites the phrase “measuring the sample contains for”; a transitional phrase appears to be missing. Appropriate correction is required.
- Claim 12 recites the phrase “bind to captured lactoferrin” and refers back to the phrase “to create a treated sample”; the term “captured” would only be applicable to a lactoferrin positive sample, the sample of claims 1, 11 and 12 need not be positive for lactoferrin. The samples of claim 1 and 11 from which claim 12 depends, have not been defined to comprise endogenous lactoferrin. Clarification of the sample type (positive for lactoferrin) is requested.

27. Claims 6-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The combination of claim limitations recited in claims 6 and 7 have been added to claim 1 by amendment; claims 6 and 7 are no longer further limiting of claim 1 from which they indirectly depend.

***Claim Rejections - 35 USC § 102***

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

29. Claims 1, 3 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al (US Pat. 6,727,073, effective filing date November 19, 1999).

Moore et al disclose and claim a method that comprises the steps of:

Obtaining a fecal sample from a person that has diarrhea, a common symptom to both inflammatory bowel disease and irritable bowel syndrome (see claim 1, “fecal liquid sample” and “a patient suffering from diarrhea”)

Measuring the sample to see if it contains an elevated level of lactoferrin, wherein a sample that is negative is diagnostic of irritable bowel syndrome (see Moore et al, col 5, lines 57 and 61-62 “Diarrhea can be caused by factors other than invasive enteric pathogens”... “has other, non-inflammatory---and hence, generally, non-pathogenic causes”. , because the sample does not contain an elevated level of lactoferrin (see Moore et al, claim 1, paragraph (c), bottom of claim 1 “neither the fecal lactoferrin antibody stripe nor the separate stripes of antibodies to organisms”.

Moore et al anticipate the instantly claimed invention as now claimed.

***Conclusion***

This is a non-final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/  
Examiner, Art Unit 1645  
July 8, 2008

/Mark Navarro/  
Primary Examiner, Art Unit 1645